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Original Article

Airflow limitations in pregnant women suspected of sleep-disordered breathing

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ABSTRACT

Background and aim: Pregnancy physiology may predispose women to the development of airflow limitations during sleep. The goal of this study was to evaluate whether pregnant women suspected of sleep-disordered breathing (SDB) are more likely to have airflow limitations compared to non-pregnant controls.

Methods: We recruited pregnant women referred for polysomnography for a diagnosis of SDB. Non-pregnant female controls matched for age, body mass index (BMI), and apnoea–hypopnoea index (AHI) were identified from a database. We examined airflow tracings for changes in amplitude and shape. We classified airflow limitation by (a) amplitude criteria defined as decreased airflow of $\geqslant$10 s without desaturation or arousal (FL 10), or decreased airflow of any duration combined with either 1–2% desaturation or arousal, (FL 1–2%); and (b) shape criteria defined as the presence of flattening or oscillations of the inspiratory flow curve.

Results: We identified 25 case-control pairs. Mean BMI was 44.0 ± 6.9 in cases and 44.1 ± 7.3 in controls. Using shape criteria, pregnant women had significantly more flow-limited breaths throughout total sleep time (32.4 ± 35.8 vs. 9.4 ± 17.9, $p < 0.0001$) and in each stage of sleep ($p < 0.0001$) than non-pregnant controls. In a subgroup analysis, pregnant women without a diagnosis of obstructive sleep apnoea (OSA) who had an AHI <5 had similar findings ($p < 0.0001$). There was no difference in airflow limitation by amplitude criteria between pregnant women and controls ($p = 0.22$).

Conclusions: Pregnant women suspected of OSA have more frequent shape-defined airflow limitations than non-pregnant controls, even when they do not meet polysomnographic OSA criteria.

1. Introduction

Changes in respiratory function during pregnancy can predispose gravid women to sleep-disordered breathing (SDB). Upper airway changes that amplify the risk of obstructive respiratory events include decreased nasal patency and increases in Mallampati score [1] and nasal congestion [2]. Other physiologic changes such as reduction in functional residual capacity also play a role by affecting airway collapsibility [3].

Snoring and obstructive sleep apnoea (OSA) have been associated with various adverse pregnancy outcomes [4]. Most studied is the association of snoring with gestational hypertensive disorders (GHDs) [5–7], a group of disorders characterised by hypertension with or without proteinuria. Women with GHD have more obstructive respiratory events during sleep than normotensive controls [8,9], and women with pre-eclampsia show a high prevalence of inspiratory airflow limitations [10,11]. As oxygen desaturations do not appear to be a prominent component of OSA in pregnancy [8,9], we speculated that gravidas suspected of OSA, including those who do not meet polysomnographic criteria for the disorder, may also have airflow abnormalities that do not meet criteria for apnoeas or hypopnoeas. Given the associations of SDB with adverse outcomes, the identification of subtle airflow

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limitations may prove to have a role in predicting adverse outcomes and may be important to recognise outside of clinically manifest pre-eclampsia.

In order to investigate the questions above, we conducted a case–control study in pregnant women suspected of SDB and matched non-pregnant controls. Our goal was to examine the prevalence of airflow limitations in pregnant women and controls and evaluate the presence of airflow limitations in a subgroup of pregnant women suspected but not diagnosed with OSA.

2. Methods

2.1. Participants

This study received approval from the Institutional Review Boards (IRBs) of both Rhode Island Hospital and Women and Infants Hospital of Rhode Island. Pregnant patients with signs and symptoms of SDB referred for in-laboratory polysomnography were recruited from an outpatient practice specialising in medical care of pregnancy and signed an informed consent. Patients on supplemental oxygen and those with a learning disability/mental retardation were excluded. Records were reviewed for adverse pregnancy outcomes. GHD was defined as elevated blood pressure on at least two recordings diagnosed after 20 weeks of gestation, with or without proteinuria. Patients with and without GHD were compared for respiratory parameters during sleep (see below).

Non-pregnant controls were identified retrospectively by reviewing databases at the sleep disorders centre. Controls were referred for polysomnography for suspicion of OSA and matched for gender, age, body mass index (BMI) and apnoea–hypopnoea index (AHI) categories of <5, 5–15, 16–30 and >30.

2.2. Polysomnography

Polysomnography data included electroencephalography, electro-oculograms from bilateral canthi, submental electromyogram, bilateral tibial electromyogram, electrocardiographic monitoring, pulse oximetry, body position, and snoring, piezoelectric strain sensors to measure chest/abdominal movement for earlier studies and inductance plethysmography for later studies according to laboratory protocol. An oronasal thermal sensor (SleepSense Nasal/Oral Thermocouple sensor, S.L.P. Inc., Elgin, IL, USA) was inserted under the nares with an oral piece adjusted over the mouth, and used to detect absence of airflow. A nasal air pressure transducer (Pro-Tech pressure Transducer Airflow – PTAF 2 or Pro-tech PTAF Lite-Respironics, Andover, MA, USA) and a DC channel was used to score hypopnoea according to American Academy of Sleep Medicine (AASM) recommendations. Low-frequency filter for nasal airflow was standardised at 0.1 Hz and high-frequency filter at 15 Hz, with a sampling rate of 100 Hz. The SomnoStar Pro (Viasys Inc., Yorba Linda, CA, USA) and XLTEC (Natus, Inc., San Carlos, CA, USA) data acquisition systems were used to record data. Patients were encouraged to sleep in the supine position and were awakened in the morning by technicians in accordance with the protocol. AHI is defined as the number of apnoeas and hypopnoeas per hour of sleep. Respiratory disturbance index (RDI) is defined as the number of apnoeas, hypopnoeas and respiratory effort-related arousals per hour of sleep.

2.3. Analysis of ventilation

Raw data were scored according to standard AASM criteria 2007 [12] by a single registered polysomnography technician who was blinded to the pregnancy status (RM). The 'Recommended' definition of hypopnoea according to the 'AASM Manual for Scoring of Sleep and Associated Events' was used [12]. Respiratory tracings were also scored for 'non-conventional' flow limitations in all subjects using two methods. The first method defined airflow limitation by reduction in amplitude as follows: (1) decreased airflow of at least 10 s, as described in previous studies [13], without desaturation or arousal (FL 10), or (2) decreased airflow for any duration but with either 1–2% oxygen desaturation or arousal (FL 1–2%) (Figs. 1A and 1B). Flow limitation index (FLI) was defined as the total number of flow limitations/total sleep time in hours. Flow limitations were scored independently by two of the co-authors (RM and GB) and assessed for inter-reader agreement.

The second method carefully assessed the shape of nasal airflow by visual analysis. A total of 10 random samples of 30-s epochs for each sleep stage (N1, N2, N3 and rapid eye movement (REM)) in each patient were selected and the percent of flow-limited breaths (number of flow-limited breaths/total number of breaths) in each epoch recorded. This method has been reported in a study assessing airflow limitation in pregnant women with pre-eclampsia [11]. Flow limitation shapes have been previously described [14,15] and an inspiratory curve was labelled as flow limited if it resembled one of these predefined shapes. Epochs with poor signal due to nasal prongs being partially or completely dislodged from the nose were discarded. Epochs in which the patient was clearly mouth breathing, evidenced by a prolonged large reduction in nasal tidal volume [VT] without a reduction in SaO_2, and no obvious signs of partial flow limitation such as oscillations or flattening in the nasal flow signal were also discarded. Epochs scored for either an arousal or an obstructive event such as apnoea, hypopnoea, or respiratory effort-related arousal were also excluded. Only polysomnograms performed on the SomnoStar Pro data acquisition systems were reviewed with this method. When one of the two subjects in the case/control pair was studied using the XLTEC data acquisition system, both subjects were then excluded.

2.4. Statistical analysis

Standard statistical analysis was performed using Microsoft Excel 2007 and STATA 10. Data are reported as means with standard deviation. Paired *t*-test was used for comparison of cases and controls. Mann–Whitney test was used in subgroup analyses. Kappa coefficient was calculated for concordance in scoring airflow limitation. Repeated measures analysis of variance (ANOVA) were used to adjust for body position.

3. Results

3.1. Patient characteristics

We recruited 25 matched case–control pairs. Mean age was 31.1 ± 5.8 in cases compared to 31.4 ± 5.8 in controls ($p = 0.64$). Mean BMI was 44.1 ± 6.9 in cases compared to 44.0 ± 7.3 in controls, $p = 0.94$. Mean gestational age at the time of polysomnography was 26.6 ± 7.6 in the pregnant group. Mean neck circumference in pregnant patients was 40.2 ± 3.4 cm but unavailable in controls. In the pregnant group, GHD and gestational diabetes were present in 24% and 44%, respectively, and all patients were obese with at least one risk factor for pre-eclampsia.

3.2. Polysomnography

Sleep measures are shown in Table 1. During the study night, there was a tendency towards less time in bed in pregnant women compared to controls. Pregnant women had significantly shorter total sleep time ($p = 0.03$) and non-rapid eye movement sleep

Fig. 1A. Example of a 90-s recording showing airflow limitation on the NPT channel associated with 1–2% desaturation on the oxygen saturation channel. FLOW indicates airflow from thermistor; NPT indicates nasal pressure transducer signal; THORACIC indicates thoracic excursion from chest belt; ABDOMINAL indicates abdominal excursion from abdominal belt; SAO2 indicates oxygen saturation from pulse oximetry.

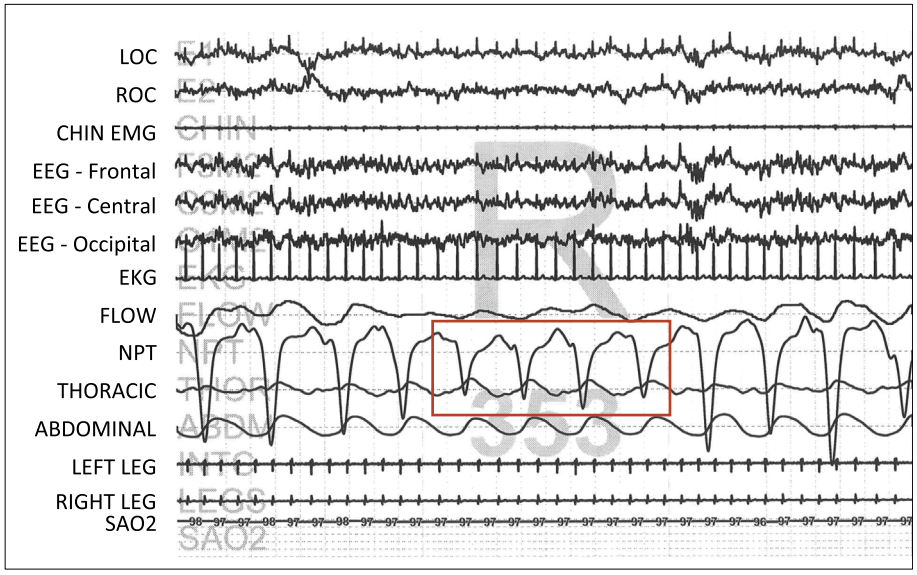

Fig. 1B. Example of a 30-s recording during rapid eye movement sleep showing airflow limitation on the NPT channel lasting 10 s or more without desaturation or arousal. LOC: left eye, ROC: right eye; CHIN EMG: chin electromyography; EEG: electroencephalography; EKG: electrocardiogram; FLOW: airflow from thermistor; NPT: nasal pressure transducer signal; THORACIC: thoracic excursion from chest belt; ABDOMINAL: abdominal excursion from abdominal belt; LEGS (right and left): lower extremity electromyography; SAO2: oxygen saturation from pulse oximetry.

compared to controls ($p = 0.02$). Mean AHI was 5.2 ± 7.7 in the pregnant group and 9.1 ± 19.1 in controls ($p = 0.32$).

When we defined OSA as AHI $\geqslant$ 5 in symptomatic pregnant patients, only eight (8/25) were diagnosed with the disorder. However, 15 women had RDI $\geqslant$ 5. There were no significant differences in age, BMI, total sleep time, AHI or RDI in the group who later developed GHD ($n = 6$) compared to the group who did not ($n = 19$).

3.3. Airflow limitations

Kappa coefficient of inter-reader agreement in scoring airflow limitations was 0.98. The majority of discrepancies for scoring FL 10 and FL 1–2% occurred in a single patient. In this case, a third investigator (RPM) helped in achieving consensus.

Examples of airflow limitation by amplitude criteria FL 10 and FL 1–2% are illustrated in Figs. 1A and 1B. There were no significant differences in FLI (using either the FL 10 or FL 1–2% definition or both) in pregnant women compared to the control group (10.1 ± 6.7 vs. 13.4 ± 11.5, $p = 0.14$), even after adjusting for body position. To evaluate whether pregnant women in whom OSA was suspected but not diagnosed had a higher prevalence of flow limitations compared to the non-pregnant subjects, we analysed the groups with AHI <5 separately. There was no significant difference in FLI between the two groups.

On the other hand, visual analysis of the shape of the breaths in 10 random 30-s epochs show a significantly higher percentage of

Table 1
Polysomnography data.

	Pregnant	Controls	*P* value
Time in bed (min)	380.3 ± 51.0	404.9 ± 44.2	0.07
TST (min)	283.6 ± 83.7	331.5 ± 73.4	0.03
TST NREM (min)	245.5 ± 66.5	290.6 ± 64.6	0.02
TST REM (min)	38.1 ± 23.0	40.9 ± 35.0	0.67
Sleep onset (min)	25.1 ± 35.3	22.5 ± 20.6	0.75
Wake after sleep onset (min)	61.3 ± 48.4	41.4 ± 25.8	0.06
Sleep efficiency (%)	72.2 ± 19.7	78.9 ± 16.9	0.19
Arousal index	20.1 ± 13.2	20.0 ± 9.5	0.98
AHI	5.2 ± 7.7	9.1 ± 19.1	0.32
RDI	12.7 ± 16.2	19.1 ± 24.5	0.16
O2 saturation mean	92.1 ± 19.3	95.7 ± 2.5	0.37
O2 saturation minimum	87.3 ± 4.6	86.3 ± 5.5	0.42

TST = total sleep time, NREM = non-rapid eye movement, REM = rapid eye movement, AHI = apnea–hypopnea index, RDI = respiratory distress index.

Table 2
Percent of flow limited breaths during sleep in cases and controls defined by shape criteria. REM: rapid eye movement.

	Cases (n = 15) %	Controls (n = 15) %	*P* value
N1 sleep	46.9 ± 37.0	12.3 ± 21.4	<0.0001
N2 sleep	36.9 ± 38.4	10.1 ± 18.4	<0.0001
N3 sleep	18.8 ± 29.1	6.3 ± 14.6	<0.0001
REM sleep	24.9 ± 30.1	9.1 ± 15.9	<0.0001
Total sleep time	32.4 ± 35.8	9.4 ± 17.9	<0.0001

flow-limited breaths in the pregnant subjects in each of the sleep stages and across total sleep time (Table 2). An example of flow-limited breaths in a pregnant patient is shown in Fig. 2. Similarly to FLI analyses, pregnant subjects without a diagnosis of OSA (AHI < 5) were compared to respective non-pregnant controls and the percent of flow-limited breaths was significantly higher in the pregnant group compared to controls, in all stages of sleep and in total sleep time. Fig. 3 illustrates the distribution of the percent of flow-limited breaths during different sleep stages and total sleep time in the subgroup of pregnant women with AHI < 5 and their respective controls. In fact, 11.2% of randomly selected epochs in total sleep time showed 100% of the breaths to be limited during inspiration by shape criteria in cases compared to 0.004% in controls. By contrast, 32.4% of selected epochs had 0% airflow limitation in cases compared to 64.1% of epochs in controls.

In an exploratory analysis. when pregnant subjects without clinically manifest pre-eclampsia who were later diagnosed with GHD were compared to those who were not, the percentage of flow-limited breaths was significantly higher in the GHD group, in stages N1 (63.6 ± 37.6 vs. 38.6 ± 33.9, $p < 0.0001$), N2 (49.3 ± 40.3 vs. 25.4 ± 32.2, $p < 0.0001$), N3 (31.5 ± 32.0 vs. 13.5 ± 26.2, $p < 0.0001$) and REM (44.6 ± 36.6 vs. 17.4 ± 21.6, $p < 0.0001$) and across total sleep time (48.8 ± 38.4 vs. 25.5 ± 32.4, $p < 0.0001$).

4. Discussion

This study evaluated the presence of subtle airflow limitations not meeting the criteria for apnoea or hypopnoea in pregnant women suspected of SDB, compared to a group of non-pregnant matched controls. We found that inspiratory airflow limitation measured by shape criteria occurred more frequently in pregnant women suspected of OSA (regardless of whether they met criteria for the disorder) compared to non-pregnant controls. Furthermore, women who were later diagnosed with GHD also had more flow limitations using shape criteria than women who did not develop the disorder. Prevalence of flow limitations defined by amplitude

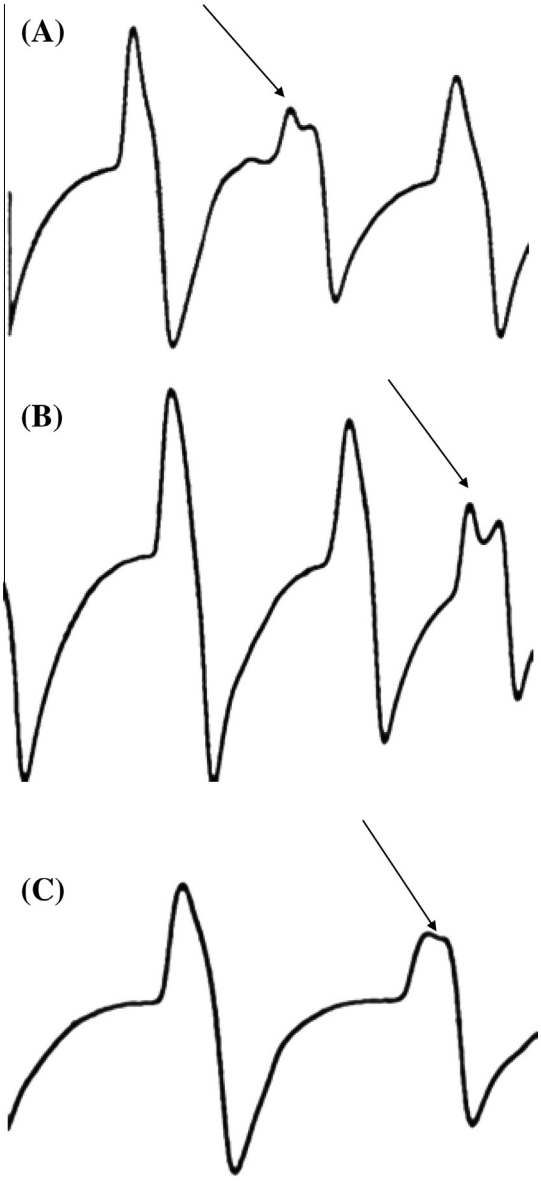

Fig. 2. Examples of three flow-limited breaths (A, B and C) in a pregnant patients.

changes were not higher in our sample of obese pregnant women compared to non-pregnant controls.

These findings provide preliminary evidence that the current scoring criteria for SDB may be inadequate for detecting clinically significant disease among pregnant women. According to AASM guidelines [12], scoring hypopnoea requires a 4% (recommended) or 3% (alternative) drop in oxygen saturation compared to baseline. Based on two other published reports and our current study, the number of pregnant women diagnosed with OSA using RDI criteria is twice the number of women diagnosed using AHI [9], and there are no significant differences in mean [8,9] or nadir oxygen saturation [8] in women with and without gestational hypertension. This finding suggests that oxygen desaturations may not be a key finding in pregnant women with adverse outcomes [8,9] and that other characteristics of SDB such as airflow limitation, arousals, or poor sleep may be potential mechanistic culprits in the association with adverse outcomes. Available data show a high prevalence of snoring [5,16] and daytime hypersomnolence [17] in the pregnant population but a relatively low prevalence of OSA in patients with high suspicion for the disorder [18]. Hence, pregnant women with

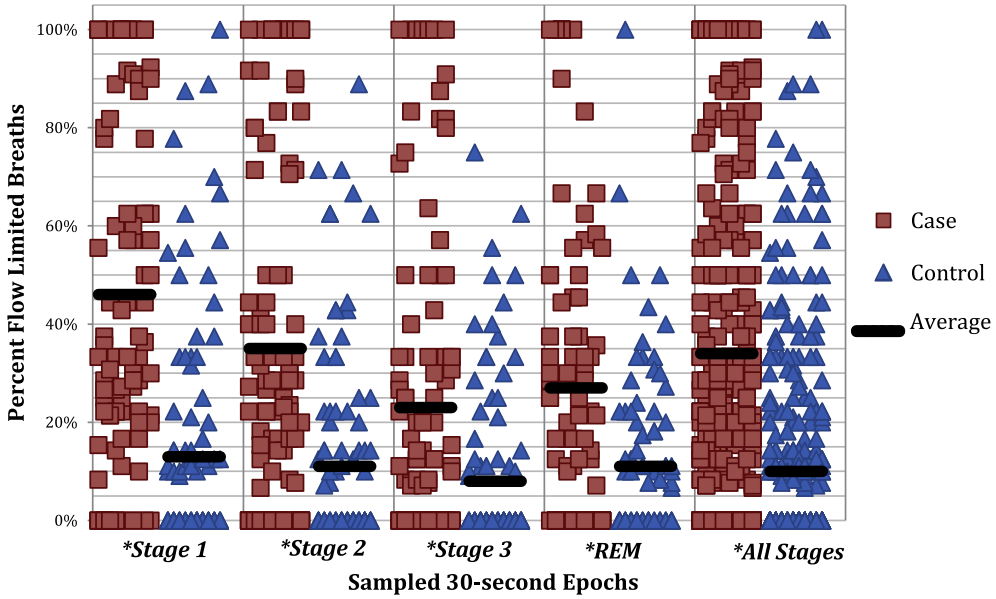

Fig. 3. Distribution of percent airflow limitation by shape criteria in randomly selected epochs in stages N1, N2, N3, rapid eye movement sleep and total sleep time. The red squares represent epochs in cases, the blue triangles represent epochs in controls and the thick black line represents the average in each sleep stage and in total sleep time. The *y*-axis indicates % airflow limited breaths per epoch. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

snoring or a suspicion of OSA may in fact have clinically significant flow limitations that do not meet the criteria for apnoeas or hypopnoeas.

The present study has shown a significantly higher prevalence of airflow-limited breaths in pregnant women compared to non-pregnant controls suspected of having OSA, even in those women who do not meet current standard diagnostic criteria for OSA and without clinical evidence of pre-eclampsia at the time of polysomnography. This is an important finding as it raises the question of whether these airflow limitations are associated with a later development of adverse pregnancy outcomes. For instance, airflow obstruction may result in a sympathetic response that could affect nocturnal blood pressure and potentially alter placental perfusion. This may be one of the mechanisms underlying the association of snoring with GHD [4]. Our data support the notion that different polysomnography scoring criteria may need to be used in the pregnant population. Using the strict definition of OSA based on AHI criteria $\geqslant 5$ may be under-diagnosing a population at risk for adverse cardiovascular outcomes such as GHDs.

Our study is an exploratory study and was not powered to assess pregnancy outcomes or the correlation of airflow limitation with such outcomes. Future research assessing the presence of airflow limitation early and late in pregnancy in women suspected of OSA and correlating these findings with the future development of adverse pregnancy outcomes are needed to examine the directionality of this potential association.

Our observation of no differences in flow limitations defined by an amplitude reduction between pregnant cases and controls may be due to our use of an airflow limitation definition that was too conservative compared to previous studies. The gold standard measurement for airflow limitations is the identification of a drop in oesophageal pressure by at least 1 cm without an accompanying increase in airflow. Although most accurate, this method is invasive and requires the placement of an oesophageal balloon. Measurement of airflow via pneumotachograph is a good method to measure flow rate [19]; however, the tight-fitting mask may be a hindrance to adequate sleep. Measurement of pressure at the nares is an appropriate method of airflow measurement [20] but may be hampered by mouth breathing. However, mouth breathing is not a common occurrence during sleep and periods of mouth breathing can usually be identified by experienced scorers. Edwards et al. [11] defined flow limitation in women with pre-eclampsia as low-frequency oscillations of 1–5 Hz in inspiratory flow on randomly selected epochs and by measurement of tidal volume with area under the curve. Similar visual analysis was performed in our study. In the study by Edwards et al., the mean percent of flow-limited breaths was higher in women with pre-eclampsia compared to our sample of pregnant women without clinically manifest GHD [11]. Others [10] used a flattening index automatically computed by the device to define flow limitation, which measured the relationship between inspiratory flow and expiratory flow duration. Guilleminault et al. defined flow limitation as a 2–30% reduction in nasal airflow signal compared to baseline [21]. Airflow limitations not meeting criteria for apnoeas or hypopnoeas were examined in the non-pregnant population [13] and in children [22]. When using the RDI definition used by Tantrakul of number of apnoeas, hypopnoeas, respiratory effort-related arousals and airflow limitation (flow reduction for 10 s), our data in pregnant women were comparable to those 316 premenopausal women in that study who were referred for polysomnography for clinical reasons. More recently, a study evaluated an epidemiological sample of asymptomatic adults who underwent polysomnography in Brazil for the presence of inspiratory flow limitation, defined as a reduction of at least four consecutive breaths that did not meet the criteria for a hypopnoea [23]. The sample consisted of 171 young individuals (mean age 36 years and 50% women). In this sample, median percent total sleep time spent with inspiratory airflow limitation was 5.09% with a confidence interval of 6.47–10.53. Although the airflow limitation definition in this study is different than ours (four breaths instead of 10 s or 1–2% desaturation or arousal), it is likely that the prevalence of airflow limitation in our sample of pregnant and non-pregnant controls suspected of sleep-disordered breathing (SDB) was significantly higher than the asymptomatic population.

Strengths of this study include the visual analysis of the entire polysomnographic studies for the identification of flow limitations and the strong agreement on flow limitation scoring among the readers.

Limitations include the retrospective identification of the control group and the shortcomings of the identification of an appropriate non-pregnant control group based on BMI, as weight distribution in pregnancy is different from the non-pregnant population. Our findings may not generalise to the entire pregnant population given the high BMIs of our pregnant participants and recruitment from a specialised pregnancy medical consultation practice.

In conclusion, this study shows that, compared to age- and BMI-matched non-pregnant controls, pregnant women suspected of OSA are more likely to have subtle airflow limitations, even when they do not meet the polysomnographic criteria of OSA.

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6. Role of sponsors

The content is entirely the responsibility of the authors, and sponsors had no role in design or conduct of the study.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.01.004.

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